Tetrahedron Vol 43, No. 21, pp 4803 to 4816, 1987
Printed in Great Britain

0040-4020/87 $3.00+.00

A NEW TOTAL SYNTHESIS OF AAPTAMINE*

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(*Received in UK* 21 *January* 1987)

Abstract - A new synthesis of the α-adrenoceptor blocker aaptamine (1) from the readily available 5-nitrovanillin is reported. An unusual intramolecular nucleophilic displacement of a nitro-group is described.

In 1982 Nakamura and co-workers[1] reported the isolation of the metabolite aaptamine (1) from the Okinawan sea sponge Aaptos aaptos. Their structural determination showed that aaptamine, which exhibits a remarkable α-adrenoceptor blocking activity, represents the first example of the heterocyclic system 1H-benzo[de]-1,6-naphthyridine (1,4-diazaphenalene). The unusual nature of the compound has focused considerable attention on its synthesis and during the course of the work described below three syntheses of aaptamine have been reported.[2,3,4] Our synthesis starts from the readily available 5-nitrovanillin and has advantages in the brevity of the route and in the absence of ambiguity in the key cyclisation step.

The reported literature methods[5] for the methylation of 5-nitrovanillin gave poor results in our hands, but use of the phase-transfer catalytic process of McKillop and co-workers[6] produced an excellent yield of the ether (2) on a multigram scale. Condensation of (2) with nitromethane in the presence of ammonium acetate gave the nitrostyrene (3) which was reduced with sodium borohydride to the saturated dinitro compound (4). Selective catalytic hydrogenation of (4) using platinum dioxide as catalyst in glacial acetic acid gave an excellent yield of the aniline (5). Reaction of (5) with dimethyl acetylenedicarboxylate gave predominantly one geometrical isomer of the adduct, from precedent[7] probably the structure shown (6). We next envisaged the cyclisation of (6) to the corresponding quinolone followed by reduction of the nitro group and ensuing ring closure of the amine to give a reduced aaptamine framework. In the event heating the

* Dedicated with warm regards to Professor Hans Wynberg on the occasion of his 65th birthday.

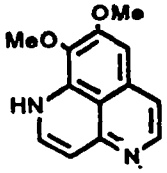
aminoacrylate (6) in diphenyl ether gave only a trace of the expected nitroquinolone. The major product obtained in 78% yield proved to be the tricyclic oxygen heterocycle (7). The formation of (7) can be rationalised by initial production of the nitroquinolone followed by an intramolecular displacement of the primary nitro group by the nucleophilic oxygen of the quinolone. Such a nucleophilic displacement involving a primary nitroalkane is a rare occurrence.[8]

In another approach to the quinolone system the nitroaniline (5) was condensed with Meldrum's acid and trimethyl orthoformate[9] to yield the anilinomethylene compound (8). Thermal cyclisation of (8) in refluxing diphenyl ether again effected extrusion of the nitro-group to yield the tricyclic oxygen heterocycle (9). This last compound could also be produced by hydrolysis and decarboxylation of (7).

To obviate this complication the following sequence was adopted. Catalytic hydrogenation of the saturated dinitro-compound (4) with Raney nickel gave the corresponding diamine[12] which was selectively acylated with benzyl chloroformate to give the mono-acylated product (10). Treatment of (10) with Meldrum's acid and trimethyl orthoformate gave the corresponding anilinomethylene compound (11). Thermal cyclisation[9] of (11) produced the quinolone (12) which was directly treated *in situ* with phosphorus oxychloride to yield the tricyclic product (13) via the intermediacy of the bicyclic chloroquinoline. Hydrogenolysis of (13) then yielded dihydroaaptamine (13; Z=H) the hydrochloride of which proved identical with the hydrogenation product of aaptamine. Direct dehydrogenation of (13; Z=H) to aaptamine under a variety of conditions proved unsuccessful. This was surprising in view of the successful dehydrogenation[2] of hexahydroaaptamine to aaptamine with palladium. In view of this unexpected hitch it was decided to employ an intermediate of higher oxidation state. Accordingly the nitroaldehyde (2) was converted into the silylated cyanohydrin (14) by treatment[10] with potassium cyanide and t-butyldimethylsilyl chloride. Hydrogenation of (14) with Raney nickel gave the corresponding amine (15) which was smoothly converted into the anilinomethylene derivative of Meldrum's acid (16). Thermal cyclisation of (16) then led to the quinolone nitrile (17). Catalytic hydrogenation of (17) with Raney nickel very efficiently reduced the nitrile group to give the corresponding primary amine. Presumably steric hindrance considerations prevented the incursion of the normally expected secondary amine by-product. The cyclisation of (18) was effected in hexamethyldisilazane solution[11] in the presence of p-toluenesulphonic acid as catalyst to yield the tricyclic product (19). This air-sensitive compound was then treated with methanolic hydrochloric acid which effected deprotection and dehydration to give aaptamine (1) as its hydrochloride. A one-pot procedure could be conveniently used to convert (18) directly into aaptamine hydrochloride. This salt was identical in all spectroscopic properties with those recorded for the natural product[1] and for previously synthesised material.[2,3,4]

EXPERIMENTAL

Analytical and preparative thin layer chromatography (t.l.c.) were carried out on plates coated with Merck Kieselgel 60 F_{254}. 'Flash' column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh). Gravity column chromatography was carried out on Merck Kieselgel 60 (70-230 mesh). Melting points were recorded on a Reichert hot stage or on a Buchi 510 instrument (sealed tube experiments), and are uncorrected. ^{1}H N.m.r. spectra were recorded at ambient probe temperature on



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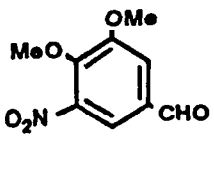

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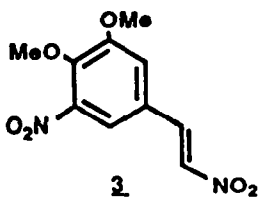

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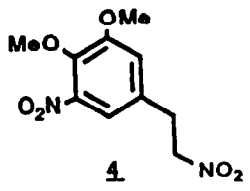

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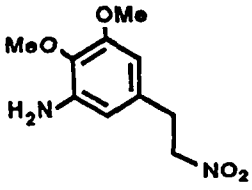

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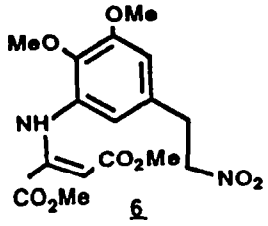

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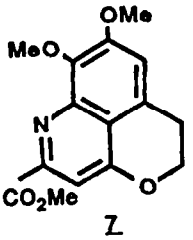

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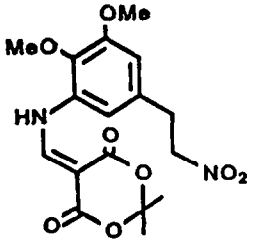

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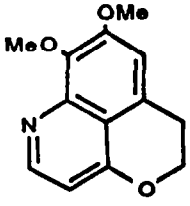

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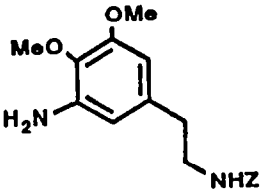

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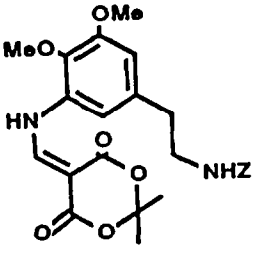

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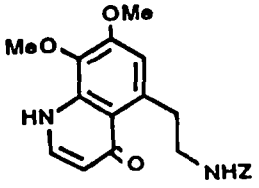

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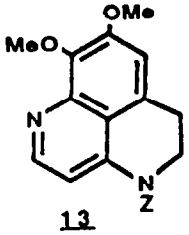

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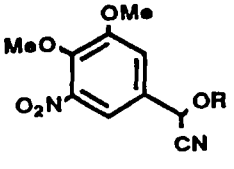

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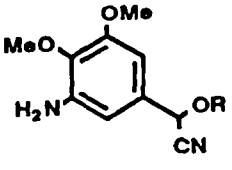

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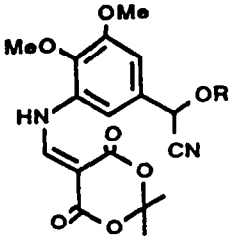

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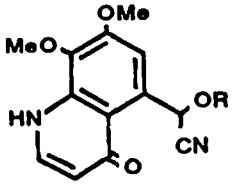

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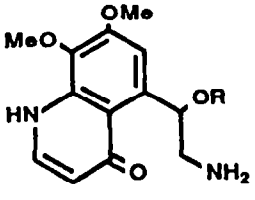

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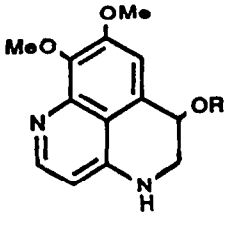

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(R = -$SiMe_2Bu^t$; Z = -CO_2CH_2Ph)

the following instruments: Varian EM360 (60 MHz) or EM390A (90 MHz), or Bruker WP80 (80 MHz) or WM250 (250 MHz). Chemical shift data for each signal are presented in units of δ relative to tetramethylsilane (TMS). ^{13}C N.m.r. spectra were recorded on a Bruker WM250 (63 MHz) machine. Chemical shift data is presented in units of δ relative to TMS. Letters in parentheses following chemical shift data refer to multiplicities observed in off-resonance decoupled spectra. Infra-red spectra were recorded in solution in chloroform (unless otherwise stated) on a Perkin-Elmer 297 or 983 spectrophotometer. U.v. spectra were recorded in solution in 95% ethanol (unless otherwise stated) on a Pye-Unican SP-100 or a Kontron Uvikon 810 instrument. Mass spectra were recorded on AEI MS902 or MS30 instruments. High resolution spectra were recorded on the MS30 in conjunction with a DS50S data system. Fast atom bombardment mass spectrometry (FAB MS) was performed using an AEI MS50 instrument. Microanalyses were performed in the University Chemical Laboratory by Mr D Flory and his staff.

3,4-Dimethoxy-5-nitrobenzaldehyde (2).

This procedure is based on the method of McKillop and co-workers.[6] A mixture of dichloromethane (250 ml), water (250 ml), 4-hydroxy-3-methoxy-5-nitrobenzaldehyde (5-nitrovanillin) (20.0 g, 102 mmol), sodium hydroxide (8.0 g, 200 mmol), benzyltributylammonium bromide (3.65 g, 10 mmol) and dimethyl sulphate (50 ml, 529 mmol) was agitated for 24 h under an atmosphere of nitrogen, and was then left to settle for 24 h to effect separation of the emulsion. The organic layer was then separated and the aqueous layer was extracted with dichloromethane (3 x 200 ml). The combined organic extracts were evaporated under reduced pressure; the residue was mixed with water and extracted with ether (2 x 500 ml). The organic extract was washed with 2N ammonia solution (2 x 250 ml) to remove dimethyl sulphate, 2N sodium hydroxide solution (2 x 200 ml) to remove unreacted phenol, brine (100 ml), was dried (Na_2SO_4), and evaporated under reduced pressure. The residual solid was purified by recrystallisation from aqueous ethanol to give 3,4-dimethoxy-5-nitrobenzaldehyde (2) (17.35 g, 81%) as cream coloured needles, m.p. 88-89 °C (lit.,[12] 90-91 °C). $\underline{R}_F$ ($CHCl_3$) 0.75; δ_H 9.91 (1H, s, CHO), 7.83 (1H, d, $\underline{J}$ = 1.8 Hz, Ar$\underline{H}$), 7.61 (1H, d, $\underline{J}$ = 1.8 Hz, Ar$\underline{H}$), 4.07 (3H, s, OCH_3), 3.99 (3H, s, OCH_3); δ_C 188.8 (CHO), 154.4, 147.4, 144.5, 131.3, 118.7, 113.7 (aromatic ring), 61.9 (OCH_3), 56.5 (OCH_3); ν_{max} 2 840 (OCH_3), 2 740 (aldehyde C-H stretch), 1 698 (aryl CHO), 1 602 (aromatic) cm^{-1}; $\underline{m/z}$ $C_9H_9NO_5$ requires $\underline{M}^+$ 211.0481, found 211.0479.

(E)-1-(3,4-Dimethoxy-5-nitrophenyl)-2-nitroethene (3).

3,4-Dimethoxy-5-nitrobenzaldehyde (2) (1.30 g, 6.2 mmol) was heated with ammonium acetate (1.2 g, 15.6 mmol) in a mixture of nitromethane (0.85 ml, 15.7 mmol) and glacial acetic acid (5.2 ml) at 100 °C for 3 h. The solvent was removed under reduced pressure leaving a brown residue which was extracted by addition of water (30 ml) and dichloromethane (2 x 30 ml). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to leave a crude yellow-brown material. The residue was purified by 'flash' column chromatography on silica gel (100 g) eluting with ethyl acetate-hexane (1:1) to give (E)-nitrostyrene (3) (1.22 g, 78%). An analytical sample was recrystallised from dilute aqueous acetic acid as yellow needles, m.p. 180-184 °C (lit.,[12] m.p. 186 °C). $\underline{R}_F$ (EtOAc) 0.64; δ_H, 7.92 (1H, d, $\underline{J}$ = 13.7 Hz, ArCH=C$\underline{H}$$NO_2$), 7.54 (1H, d, $\underline{J}$ = 13.7 Hz, Ar$\underline{C}$H=CHNO_2), 7.54 (1H, d, $\underline{J}$ = 2.0 Hz, Ar$\underline{H}$), 7.18 (1H, d, $\underline{J}$ = 2.0 Hz,

ArH), 4.04 (3H, s, OCH_3), 3.98 (3H, s, OCH_3); ν_{max} 2 840 (OCH_3), 1 640 (C=C), 1 605 (aromatic), 1 550-1 520 (NO_2), 1 370-1 350 (NO_2) cm^{-1}; λ_{max}, 320 (ε = 3 900), 260 sh (4 500) nm; m/z $C_{10}H_{10}N_2O_6$ requires M^+ 254.0539, found 254.0538.

1-(3,4-Dimethoxy-5-nitrophenyl)-2-nitroethane (4).

(E)-1-(3,4-Dimethoxy-5-nitrophenyl)-2-nitroethene (3) (0.1 g, 0.4 mmol) was dissolved in methanol (10 ml) and ethyl acetate (4 ml) by heating. The flask was then placed in an ice-bath and portions of sodium borohydride (0.15 g, 4 mmol) were added over 5 min with stirring. After 15 min, hydrochloric acid (2N) was added dropwise until the solution was permanently acidic to universal indicator paper, and then the solvent was removed under reduced pressure. Water (15 ml) and dichloromethane (2 x 20 ml) were added, and the combined organic extracts were washed with water (10 ml), and with brine (5 ml), dried (Na_2SO_4), and finally evaporated under reduced pressure to give a yellow gum in nearly quantitative yield. The gum was purified by 'flash' column chromatography on silica gel (20 g) eluting with dichloromethane-hexane (10:1) to give the nitroethane (4) (0.093 g, 92%) as a yellow solid, m.p. 85-93 °C. This material was sufficiently pure to be used in later steps, but an analytical sample was also prepared by slow evaporation from a dichloromethane-hexane solution, as pale yellow needles, m.p. 93-95 °C. R_F (EtOAc) 0.60. $C_{10}H_{12}N_2O_6$ requires C, 46.88; H, 4.72; N, 10.94; M, 256.0696. Found: C, 46.81; H, 4.84; N, 10.77; M^+ 256.0685; δ_H 7.18 (1H, d, J = 1.7 Hz, ArH), 6.93 (1H, d, J = 1.7 Hz, ArH), 4.63 (2H, t, J = 6.9 Hz, $CH_2CH_2NO_2$), 3.95 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.31 (2H, t, J = 6.9 Hz, $CH_2CH_2NO_2$); ν_{max} 2 830 (OCH_3), 1 603 (aromatic), 1 550 (NO_2), 1 360 (NO_2) cm^{-1}; λ_{max} 316 sh (ε = 1 150), 245 sh (4 000) nm; m/z 256 (29%, M^+), 210 (18, M - NO_2), 209 (100, M - HNO_2).

2,3-Dimethoxy-5-(2-nitroethyl)aniline (5).

Adams' catalyst (50 mg) was prehydrogenated in glacial acetic acid (10 ml) at room temperature and pressure for 30 min. 1-(3,4-Dimethoxy-5-nitrophenyl)-2-nitroethane (4) (150 mg, 0.59 mmol) was added and the reaction mixture was hydrogenated at room temperature and pressure. After 3 h, the theoretical volume of hydrogen gas for mono-reduction had been absorbed, and analytical t.l.c. indicated the formation of a single product. The reaction mixture was filtered through celite, washed through with glacial acetic acid (5 x 5 ml), and the filtrate was evaporated under reduced pressure. The residue was purified by 'flash' column chromatography on silica gel (10 g) eluting with ethyl acetate-hexane (1:1) to give the nitroethylaniline (5) (126 mg, 95%) as a yellow, syrupy oil. R_F [EtOAc-hexane (1:1)] 0.31. $C_{10}H_{14}N_2O_4$ requires C, 53.09; H, 6.24; N, 12.38; M 226.0953. Found: C, 52.80; H, 6.44; N, 12.10; M^+ 226.0940; δ_H 6.21 (1H, d, J = 1.8 Hz, ArH), 6.14 (1H, d, J = 1.8 Hz, ArH), 5.2-5.0 (2H, br s, NH), 4.56 (2H, t, J = 7.5 Hz, $ArCH_2CH_2NO_2$), 3.81 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.16 (1H, t, J = 7.5 Hz, $ArCH_2CH_2NO_2$); ν_{max} 3 490 (NH), 3 396 (NH), 2 995, 2 938 (CH), 2 846, 2 835 (OCH_3), 1 598 (aromatic or NH_2 bend), 1 553 (NO_2), 1 512, 1 359 (NO_2) cm^{-1}; λ_{max} 284 (ε = 1 352), 230 sh (3 700), 212 (20 600) nm; m/z 226 (59%, M^+), 211 (4, M - CH_3), 180 (22, M - NO_2), 179 (40, M - HNO_2), 164 (100, M - CH_2NO_2).

Dimethyl 2-[2,3-dimethoxy-5-(2-nitroethyl)phenylamino]but-2-enedioate (6).

Dimethyl acetylenedicarboxylate (50 µl, 0.41 mmol) was added dropwise over 5 min to a stirred solution of nitroethylaniline (5) (43 mg, 0.19 mmol) in methanol (20 ml) under nitrogen at room temperature. After 12 h, the solvent was evaporated

under reduced pressure and the residue was purified by 'flash' column chromatography on silica gel (10 g) eluting with ethyl acetate-light petroleum (b.p. 40-60 °C) (1:2) to give the enamine (6) (54 mg, 77%) as a yellow gum. R_F [EtOAc-Hexane (1:1)] 0.43; $C_{16}H_{20}N_2O_8$ requires C, 52.17; H, 5.47; N, 7.61; M 368.1220. Found: C, 52.03; H, 5.72; N, 7.79; M^+ 368.1230. δ_H 9.54 (1H, s, NH), 6.46 (1H, d, J = 1.8 Hz, ArH), 6.29 (1H, d, J = 1.8 Hz, ArH), 5.46 (1H, s, C=CHCO$_2$Me), 4.56 (2H, t, J = 7.2 Hz, ArCH$_2$CH$_2$NO$_2$), 3.83 (3H, s, OCH$_3$), 3.73 (3 x 3H, s, 3 x OCH$_3$), 3.19 (2H, t, J = 7.2 Hz, ArCH$_2$CH$_2$NO$_2$); δ_C 169.7 (CO$_2$Me), 164.5 (CO$_2$Me), 153.4, 147.5, 139.8, 134.8, 131.5, 113.3, 108.6, 94.1 (6 x ring carbons and 2 x vinyl carbons), 76.1 (CH$_2$NO$_2$), 60.5, 56.1, 52.7, 51.1 (4 x OCH$_3$), 33.4 (ArCH$_2$); ν_{max} 3 296 (NH), 2 953 (CH), 2 845 (OCH$_3$), 1 735 (ester C=O), 1 668 (C=C), 1 554 (NO$_2$), 1 380, 1 360 (NO$_2$) cm^{-1}; λ_{max} 329 (ε = 13 100), 216 (22 200); m/z 368 (100%, M^+), 309 (67, M - CO$_2$CH$_3$).

Methyl 7,8-dimethoxy-5-(2-nitroethyl)-4(1H)-quinolone-2-carboxylate and **methyl 5,6-dihydro-8,9-dimethoxypyrano[2,3,4-de]quinoline-2-carboxylate** (7).

Enamine (6) (44 mg, 0.12 mmol) was dissolved in warm diphenyl ether (4 ml) in a round bottomed flask. The flask was fitted with an air condenser and the apparatus was flushed with a stream of nitrogen. The flask was immersed in a preheated Wood's metal bath, which was maintained at a high temperature to ensure rapid refluxing. After 2 min the flask was removed from the bath and allowed to cool to room temperature. The crude reaction mixture was purified by 'flash' column chromatography on silica gel (diameter 2 cm x 20 cm), applying the reaction mixture to the column with dichloromethane (4 ml) and eluting first with hexane (250 ml) (to remove diphenyl ether), then ethyl acetate-hexane (1:1) graduating to ethyl acetate. The faster running fraction was triturated with methanol and dried in vacuo to give the quinolone (2 mg, 5%) as pale yellow rods, m.p. 130-132 °C. R_F (EtOAc) 0.46. $C_{15}H_{16}N_2O_7$ requires C, 53.57; H, 4.80; N, 8.33; M 336.0957. Found; C, 53.49; H, 4.77; N, 8.15; M^+ 336.0947. δ_H 9.29 (1H, br, NH), 6.80 (1H, d, J = 2.0 Hz, 3-H), 6.75 (1H, s, 6-H), 4.79 (2H, t, J = 6.3 Hz, ArCH$_2$CH$_2$NO$_2$), 4.02 (3H, s, OCH$_3$), 4.01 (3H, s, OCH$_3$), 3.97 (3H, s, OCH$_3$), 3.88 (2H, t, J = 6.3 Hz, ArCH$_2$CH$_2$NO$_2$); ν_{max} 3 389 (NH), 2 987, 2 957, 2 942 (CH), 2 853 (OCH$_3$), 1 727 (conj. ester C=O), 1 628 (quinolone), 1 610 (aromatic), 1 590 (aromatic), 1 548 (NO$_2$), 1 463, 1 438, 1 377, 1 367 (NO$_2$) cm^{-1}; λ_{max} 335 (ε = 4 700), 283 (7 000), 272 (7 300), 227 (22 700), 204 (19 200) nm; m/z 336 (0.35%, M^+), 290 (100, M - NO$_2$).

The slower running fraction was evaporated, triturated with methanol and dried in vacuo to give the tricyclic ester (7) (27 mg, 78%) as pale yellow plates, m.p. 175-176 °C. R_F (EtOAc) 0.36. $C_{15}H_{15}NO_5$ requires C, 62.28; H, 5.23; N, 4.8%; M 289.0950. Found: C, 62.35; H, 5.30; N, 4.76; M^+ 289.0938. δ_H 7.47 (1H, s, ArH), 7.10 (1H, s, ArH), 4.50 (2H, t, J = 5.8 Hz, CH$_2$CH$_2$O), 4.18 (3H, s, CO$_2$CH$_3$), 4.08 (3H, s, OCH$_3$), 4.01 (3H, s, OCH$_3$), 3.24 (2H, t, J = 5.8 Hz, ArCH$_2$CH$_2$); ν_{max} 2 856 (OCH$_3$), 1 722 (ester C=O), 1 607 (aromatic), 1 511 (aromatic) cm^{-1}; λ_{max} 354 (ε = 2 800), 298 (3 700), 254 (40 900), 220 (20 500) nm; m/z 289 (29%, M^+), 288 (73, M - H), 274 (100, M - CH$_3$), 260 (40, M - CHO); FAB 290 (MH^+).

5-[2,3-Dimethoxy-5-(2-nitroethyl)phenylaminomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (8).

2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (195 mg, 1.35 mmol) and trimethyl orthoformate (5 ml) were refluxed for 2 h. Then a solution of

nitroethylaniline (5) (300 mg, 1.33 mmol) in trimethyl orthoformate (5 ml) was added and the reaction mixture was refluxed for a further 3 h. The solvent was evaporated under reduced pressure, and the residue was purified by 'flash' column chromatography on silica gel (20 g) eluting with ethyl acetate-hexane (1:1) to give the Meldrum's acid derivative (8) (461 mg, 91%) as a pale yellow microcrystalline solid, m.p. 147-149 °C. This material was sufficiently pure to use in the next step; an analytical sample was prepared by recrystallisation from methanol, as pale yellow needles, m.p. 148-150 °C. R_F [EtOAc-hexane (1:1)] 0.23. $C_{17}H_{20}N_2O_8$ requires C, 53.68; H, 5.30; N, 7.37; M 380.1220. Found: C, 53.94; H, 5.38; N, 7.13; M^+ 380.1194. δ_H 10.15 (1H, br d, J = 14.6 Hz, NH), 8.61 (1H, d, J = 14.6 Hz, NH-CH=C), 6.81 (1H, d, J = 1.5 Hz, ArH), 6.60 (1H, d, J = 1.5 Hz, ArH), 4.63 (2H, t, J = 7.0 Hz, $ArCH_2CH_2NO_2$), 3.93 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.28 (2H, t, J = 7.0 Hz, $ArCH_2CH_2NO_2$), 1.74 [6H, s, $(CH_3)_2C$]; ν_{max} 3 252 (NH), 3 183 (NH), 2 990, 2 971, 2 942 (CH), 2 841 (OCH_3), 1 725, 1 678 (conj. C=O), 1 616 (C=C), 1 598 (aromatic), 1 554 (NO_2), 1 509 (aromatic), 1 378, 1 333 (NO_2) cm^{-1}; λ_{max} 336 (ε = 22 000), 250 sh (7 300), 233 (13 500) nm; m/z 380 (29, M^+), 322 (25, M - acetone), 247 (100, M - OCH_3 - CO_2 - acetone), 231 (91, M - CO_2 - acetone - HNO_2); FAB 381 (MH^+).

5,6-Dihydro-8,9-dimethoxypyrano[2,3,4-de]quinoline (9).

Method 1. Meldrum's acid derivative (8) (77 mg, 0.20 mmol) was refluxed in diphenyl ether (5 ml) under a stream of nitrogen on a preheated Wood's metal bath. After 5 min the reaction mixture was cooled, and was purifed by flash column chromatography on silica gel (diameter 3 cm x 20 cm) applying the reaction mixture to the column with dichloromethane (2 ml) and eluting first with hexane (300 ml) (to remove diphenyl ether), then sequentially with ethyl acetate-hexane (1:2), (1:1), (2:1) and finally ethyl acetate to give a gum. This was triturated with methanol and then dried in vacuo to give the tricyclic product (9) (31 mg, 66%) as cream microcrystals , m.p. 74-76 °C. R_F (EtOAc) 0.21 (UV, $KMnO_4$). $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.06; M 231.0895. Found: C, 67.63; H, 5.77; N, 6.14; M^+ 231.0876. δ_H 8.77 (1H, d, J = 5.3 Hz, 2-H), 7.04 (1H, d, J = 0.9 Hz, 7-H), 6.73 (1H, d, J = 5.3 Hz, 3-H), 4.50 (2H, J = 5.9 Hz, $ArCH_2CH_2O$), 4.08 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 3.24 (2H, dt, J = 0.9 Hz, 5.3 Hz, $ArCH_2CH_2O$); δ_C 152.7, 151.0, 125.9, 113.4, 112.2, 112.2, 104.0 (7 x aromatic C: 2 x C absent), 67.1 (CH_2O), 61.9 (OCH_3), 57.2 (OCH_3), 28.2 ($ArCH_2$); ν_{max} 2 935 (CH), 2 850 (OCH_3), 1 609 (aromatic), 1 506 (aromatic), 1 476, 1 462, 1 408, 1 368, 1 327, 1 306, 1 117, 1 009, 908 cm^{-1}; λ_{max} 334 (ε = 7 600), 305 (8 300), 291 (7 900) nm; m/z 231 (34%, M^+), 230 (63, M - H), 216 (100, M - CH_3), 202 (48, M - CHO); FAB 232 (MH^+).

Method 2. Methyl ester (7) (43 mg, 0.15 mmol) and potassium hydroxide (45 mg, 0.33 mmol) were stirred in a mixture of methanol (5 ml) and water (5 ml) at room temperature. After 12 h, the solution was acidified with hydrochloric acid (2M), and the solvent was removed by evaporation under reduced pressure. Hydrochloric acid (10 ml of 1M) and dichloromethane (2 x 25 ml) were added and shaken, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was taken up in diphenyl ether (5 ml) and heated at 180 °C. After 30 min, the reaction mixture was cooled to room temperature, diluted with dichloromethane (15 ml), and extracted with hydrochloric acid (2 x 10 ml of 3M). The combined aqueous extracts were made alkaline by the addition of potassium hydroxide solution (2N) and were extracted with

dichloromethane (2 x 10 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by preparative t.l.c. on silica gel eluting with ethyl acetate to give the decarboxylated tricyclic product (**9**) (19 mg, 55%) identical to material prepared as above.

Benzyl 2-(5-amino-3,4-dimethoxyphenyl)ethylcarbamate (10).

Benzyl chloroformate (714 µl, 5 mmol) was added dropwise to a stirred solution of 2-(5-amino-3,4-dimethoxyphenyl)ethylamine[12] (980 mg, 5 mmol) and potassium carbonate (1 g, 7.2 mmol) in dry dichloromethane (150 ml) under nitrogen at 0 °C. After 2 h, the reaction mixture was washed with water (100 ml), with sodium hydrogen carbonate (100 ml), with brine (50 ml), and dried (Na_2SO_4). The organic extract was evaporated under reduced pressure and the residue was purified by 'flash' column chromatography on silica gel (100 g) eluting with ethyl acetate-hexane (1:1) to give, as the slower running product, the mono-acylated-derivative (**10**) (1190 mg, 72%) as a syrupy oil. R_F [EtOAc-hexane (3:2)] 0.30. $C_{18}H_{22}N_2O_4$ requires C, 65.44; H, 6.71; N, 8.48; M, 350.1580. Found: C, 65.17; H, 6.82; N, 8.64; M^+ 330.1569. δ_H 7.34 (5H, m, $PhCH_2O$), 6.19 (1H, d, J = 2.0 Hz, ArH), 6.13 (1H, d, J = 2.0 Hz, ArH), 5.09 (2H, s, CH_2Ph), 4.80 (1H, br t, J = 6.0 Hz, CH_2NHCO_2Bz), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.6-2.7 (2H, br, NH_2), 3.41 (2H, dt, J = 6.0 Hz, 6.8 Hz, $ArCH_2CH_2NHZ$), 2.65 (2H, t, J = 6.8 Hz, $ArCH_2CH_2NHZ$); ν_{max} 3 450 (NH), 3 395 (NH), 2 845 (OCH_3), 2 834 (OCH_3), 1 722 (carbamate C=O), 1 597 (aromatic or NH_2 bend), 1 500 (aromatic) cm^{-1}; λ_{max} 283 (ε = 1 200), 229 sh (9 700), 212 (41 300) nm; m/z 330 (51, M^+), 179 (55, M - $BzOCONH_2$), 91 (100, $PhCH_2^+$).

The faster running fractions gave the bis-acylated-derivative (137 mg, 6%) as a syrupy oil. R_F [EtOAc-hexane (3:2)] 0.45. $C_{26}H_{28}N_2O_6$ requires C, 67.23; H, 6.08; N, 6.03; M 464.1948. Found: C, 67.01; H, 6.15; N, 6.13; M^+ 464.1967.

5-{5-[2-(Benzyloxycarbonylamino)ethyl]-2,3-dimethoxyphenylaminomethylene}-2,2-dimethyl-1,3-dioxane-4,6-dione (11).

2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (322 mg, 2.24 mmol) and trimethyl orthoformate (10 ml) were refluxed for 2 h. Then a solution of monobenzyl carbamate (**10**) (438 mg, 1.33 mmol) in trimethyl orthoformate (10 ml) was added and the reaction mixture was refluxed for a further 3 h. The solvent was evaporated under reduced pressure, and the residue was purified by 'flash' column chromatography on silica gel (50 g) eluting with ethyl acetate-hexane (3:2) to give the Meldrum's acid derivative (**11**) (599 mg, 93%) as needles, m.p. 124-126 °C. R_F [EtOAc-hexane (3:2)] 0.30. $C_{25}H_{28}N_2O_8$ requires C, 61.98; H, 5.83; N, 5.78; M 484.1846. Found: C, 61.94; H, 5.98; N, 5.62; M^+ 484.1855. δ_H 11.65 (1H, br d, J = 15 Hz, NH-CH=C), 8.70 (1H, d, J = 15 Hz, NH-CH=C), 7.45-7.25 (5H, m, $PhCH_2O$), 6.80 1H, d, J = 2 Hz, ArH), 6.65 (1H, d, J = 2 Hz, ArH), 5.10 (2H, s, CH_2Ph), 5.10-4.70 (1H, br NH), 3.95 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.40 (2H, t, J = 7 Hz, $ArCH_2CH_2NH$), 2.80 (2H, t, J = 7 Hz, $ArCH_2CH_2NH$), 1.70 [6H, s, $(CH_3)_2C$]; ν_{max} 3 448 (NH), 3 250 (NH), 3 171 (NH), 2 840 (OCH_3), 1 720 (carbamate C=O), 1 676 (conj. C=O), 1 617 (C=C), 1 598 (aromatic), 1 506 (aromatic) cm^{-1}; λ_{max} 334 (ε= 20 900), 254 sh (6 400), 231 (13 900) nm; m/z 484 (0.9%, M^+), 426 (8, M - acetone), 382 (2, M - acetone - CO_2), 231 (98, M - acetone - CO_2 - $PhCH_2OCONH_2$), 216 [100, (231-CH_3)].

Benzyl 2-[7,8-dimethoxy-4(1H)-quinolinon-5-yl]ethylaminocarboxylate (12).

Meldrum's acid derivative (11) (280 mg, 0.58 mmol) was refluxed in diphenyl ether (5 ml) under a stream of nitrogen in a preheated Wood's metal bath. After 10 min, the reaction mixture was cooled, and was purified by 'flash' column chromatography on silica gel (20 g), applying the reaction mixture to the column with dichloromethane (2 ml), and eluting first with hexane, then sequentially with ethyl acetate-hexane (1:1), ethyl acetate, and finally ethyl acetate-methanol (95:5) to give the Z-protected quinolone (12) (152 mg, 69%) as plates, m.p. 194-196 °C. R_F (EtOAc) 0.15. $C_{21}H_{22}N_2O_5$ requires C, 65.96; H, 5.80; N, 7.33; M 382.1529. Found: C, 66.20; H, 5.68; N, 7.35; M^+ 382.1557. δ_H (d_6-DMSO) 11.05 (1H, br s, NH), 7.63 (1H, br d, J = 7.4 Hz, 2-H), 7.34-7.26 (5H, m, $PhCH_2$), 6.95 (1H, br, NH), 6.79 (1H, s, 6-H), 5.89 (1H, d, J = 7.4 Hz, 3-H), 4.96 (2H, s, $PhCH_2O$), 3.86 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.39 (2H, t, J = 5.6 Hz, $ArCH_2CH_2NH$), 3.29 (2H, t, J = 5.6 Hz, $ArCH_2CH_2NH$); ν_{max} 3 419 (quinolone NH), 3 301 (carbamate NH), 2 851 (OCH_3), 1 708 (carbamate C=O), 1 627 (quinolone), 1 612 (quinolone), 1 585 (aromatic), 1 528, 1 508, 1 458, 1 430, 1 307, 1 285, 1 266, 1 256, 1 248, 1 161 cm^{-1}; λ_{max} (MeOH) 331 sh (ε = 7 400), 322 (8 200), 264 (18 100), 257 (16 500), 235 sh (20 300), 226 (26 800), 218 (22 400) nm; m/z 382 (24%, M^+), 274 (10, M - $PhCH_2OH$), 216 (100); FAB 383 (MH^+).

N-Benzyloxycarbonyl-5,6-dihydroaaptamine (13).

Method 1. Meldrum's acid derivative (11) (1.20 g, 2.5 mmol) was refluxed in diphenyl ether (5 ml) under a stream of nitrogen on a preheated Wood's metal bath. After 4 min, the reaction mixture was cooled, the air condenser was replaced by a water condenser and phosphorus oxychloride (1 ml, 10.7 mmol) was added. The reaction mixture was then heated at 145 °C for 45 min, and recooled. Ether (200 ml) and aqueous hydrochloric acid (200 ml of a 2M solution) were added; the aqueous layer was extracted, washed with ether (200 ml) and then made alkaline by the addition of saturated sodium carbonate solution. The aqueous phase was then extracted with ethyl acetate (3 x 200 ml), and the combined organic extracts were washed with brine (100 ml), dried (Na_2SO_4) and evaporated under reduced pressure to give a gum. The residue was purified by 'flash' column chromatography on silica gel (100 g) eluting with ethyl acetate to give the N-benzyloxycarbonyl-5,6-dihydroaaptamine (13) (569 mg, 63%) as platelets, m.p. 121-123 °C. R_F (EtOAc) 0.26. $C_{21}H_{20}N_2O_4$ requires C, 69.22; H, 5.53; N, 7.69; M 364.1423. Found: C, 69.27; H, 5.57; N, 7.50; M^+ 364.1423. δ_H 8.79 (1H, d, J = 5.2 Hz, 2-H), 7.72 (1H, d, J = 5.2 Hz, 3-H), 7.43-7.37 (5H, m, Ph), 7.05 (1H, s, 6-H), 5.32 (2H, s, CH_2Ph), 4.15 (2H, t, J = 5.6 Hz, CH_2NZ), 4.07 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 3.16 (2H, t, J = 5.6 Hz, $ArCH_2CH_2NZ$); ν_{max} 2 941 (CH), 2 857 (CH), 1 710 (carbamate C=O), 1 609 (aromatic), 1 505 (aromatic), 1 477, 1 463, 1 410, 1 304 cm^{-1}; λ_{max} 339 (ε = 5 800), 313 (6 500), 303 (5 300), 264 (13 200), 244 (50 900) nm; m/z 364 (3.65%, M^+), 349 (3, M - CH_3), 91 (100, $PhCH_2^+$); FAB 365 (MH^+).

Method 2. Benzyloxycarbonylaminoethylquinolone (12) (280 mg, 0.73 mmol) and phosphorus oxychloride (0.5 ml) were refluxed under nitrogen. After 45 min, the solvent was evaporated under reduced pressure. Ether (50 ml) and aqueous hydrochloric acid (50 ml of a 2M solution) were added; the aqueous layer was extracted, washed with ether (50 ml) and then made alkaline by the addition of saturated sodium carbonate solution. The aqueous phase was extracted with ethyl acetate (3 x 50 ml), and the combined organic extracts were washed with brine (20

ml), dried (Na_2SO_4) and evaporated under reduced pressure to give a gum. The residue was purified by 'flash' column chromatography on silica gel (20 g) eluting with ethyl acetate to give the benzyloxycarbonyldihydroaaptamine (13) (214 mg, 80%) identical to material prepared by method 1.

5,6-Dihydroaaptamine (13; Z=H).

Benzyloxycarbonyldihydroaaptamine (13) (480 mg, 1.32 mmol) was hydrogenated at room temperature and pressure in methanol (150 ml) with 10% palladium-on-carbon as catalyst. After 12 h, the reaction mixture was filtered through celite, washed with methanol (3 x 150 ml), and the filtrate was evaporated under reduced pressure. The residue was recrystallised from ethyl acetate to give dihydroaaptamine (4) (256 mg, 84%) as a microcrystalline solid, m.p. 182-185 °C. $C_{13}H_{14}N_2O_2$ requires M 230.1055. Found M^+ 230.1039. δ_H (d_6-DMSO) 8.22 (1H, d, $J_{2,3}$ = 5.2 Hz, H-2), 7.17 (1H, br s, H-4), 7.02 (1H, s, H-7), 6.32 (1H, d, $J_{2,3}$ = 5.2 Hz, H-3), 3.88 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.39 (2H, dt, $J_{4,5}$ = 1.9 Hz and $J_{5,6}$ = 6.2 Hz, 2 x H-5), 3.03 (2H, t, $J_{5,6}$ = 6.2 Hz, 2 x H-6); δ_C (CD_3OD) 153.8 (s), 153.7 (s), 150.3 (d), 143.6 (s), 141.2 (s), 130.6 (s), 113.3 (s), 111.3 (d), 100.7 (d), 61.6 (q), 57.2 (q), 41.2 (t), 29.4 (t); ν_{max} (KBr disc) 3 413 (NH), 3 241 (NH), 3 173 (NH), 3 096, 3 065, 2 990, 2 960, 2 936, 2 849 (OCH_3), 2 832 (OCH_3), 1 603, 1 525, 1 479, 1 457, 1 443, 1 419, 1 387, 1 342, 1 324, 1 314, 1 298, 1 231, 1 202, 1 119, 1 027, 864, 836. The strongest absorbances below 2 000 were: 1 603, 1 525, 1 342, 1 298, 1 119, 1 027, 836 cm^{-1}; λ_{max} (MeOH) 336 (ϵ = 8 200), 324 (8 500), 284 (8 200), 276 (7 500), 242 sh (26 700), 238 (27 700) nm; m/z 230 (40.0%, M^+), 229 (87.8, M - H), 215 (100, M - CH_3), 213 (22), 201 (56, M - CHO), 199 (43, M - OCH_3).

The dihydroaaptamine showed complete identity in five t.l.c. solvent systems with an authentic sample. The free base was treated with hydrogen chloride in methanol and recrystallised from a mixture of methanol and acetone to give 5,6-dihydroaaptamine hydrochloride in 82% yield as pale yellow needles, m.p. 229-231 °C (authentic sample, m.p. 228-231 °C; mixed m.p. 228-231 °C) (sealed tube experiments). $C_{13}H_{15}N_2O_2Cl.H_2O$ requires C, 54.84; H, 6.02; N, 9.74. Found: C, 55.08; H, 5.82; N, 9.69. δ_H (d_6-DMSO) 12.82 (1H, br d, $J_{1,2}$ = 6.5 Hz, H-1), 9.64 (1H, br d, $J_{4,5}$ = 1.3 Hz, H-4), 8.13 (1H, dd, $J_{1,2}$ = 6.5 Hz and $J_{2,3}$ = 6.9 Hz, H-2), 7.36 (1H, s, H-7), 6.59 (1H, d, $J_{2,3}$ = 6.9 Hz, H-3), 4.01 (3H, s, CH_3O-8), 3.88 (3H, s, CH_3O-9), 3.64 (2H, dt, $J_{4,5}$ = 1.3 Hz and $J_{5,6}$ = 6.8 Hz, 2 x H-5), 3.14 (2H, t, $J_{5,6}$ = 6.8 Hz, 2 X H-6); δ_C (CD_3OD) 157.4 (s), 156.5 (s), 141.6 (d), 136.0 (s), 134.3 (s), 131.7 (s), 112.5 (d), 109.7 (s), 100.6 (d), 61.9 (q), 57.4 (q), 41.0 (t), 27.2 (t).

2-(t-Butyldimethylsilyloxy)-2-(3,4-dimethoxy-5-nitrophenyl)ethanonitrile (14).

3,4-Dimethoxy-5-nitrobenzaldehyde (2) (5.34 g, 25.3 mol) acetonitrile (75 ml), potassium cyanide (5.6 g, 81 mmol), zinc iodide (100 mg, 0.3 mmol) and t-butyldimethylsilyl chloride (6.0 g, 39.8 mmol) were added in succession to a flame dried flask, maintained under a positive pressure of argon and the mixture was stirred vigorously. After 48 h the solvent was removed under reduced pressure, and the residue was resuspended in ether (250 ml). The mixture was filtered to remove salts, and then washed through with more ether (2 x 250 ml). The filtrate was washed with water (100 ml), brine (50 ml), dried (Na_2SO_4), and evaporated under reduced pressure to give an orange oil which was purified by 'flash' column chromatography on silica gel (50 g) eluting with ethyl acetate-hexane (1:3) to give

the silylated cyanohydrin (14) (7.35 g, 83%) as pale yellow needles, m.p. 54-55 °C. R_F [EtOAc-hexane (1:1)] 0.63. $C_{16}H_{24}N_2O_5Si$ requires C, 54.52; H, 6.86; N, 7.95; M 352.1455. Found: C, 54.67; H, 6.83; N, 8.01; M^+ 352.1445. δ_H 7.40 (1H, d, J = 1.7 Hz, ArH), 7.21 (1H, d, J = 1.7 Hz, ArH), 5.48 [1H, s, ArCH(OSi)CN], 3.99 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 0.95 [9H, s, $(CH_3)_3CSi$], 0.25 (3H, s, CH_3Si), 0.18 (3H, s, CH_3Si); ν_{max} 2 885 (CH), 2 859 (OCH_3), 1 611 (aromatic), 1 541 (NO_2), 1 534 (NO_2), 1 495 (aromatic), 1 389 (t-Bu), 1 361 (NO_2) cm^{-1}; λ_{max} 321 (ε = 2 000), 260 (2 900), 223 (13 700) nm; m/z 352 (2.2%, M^+), 337 (2, M - CH_3), 295 (94, M - t-Bu), 89 (100).

2-(5-Amino-3,4-dimethoxyphenyl)-2-(t-butyldimethylsilyloxy)ethanonitrile (15).

Nitrophenylsilylcyanohydrin (14) (184 mg, 0.52 mmol) was hydrogenated with W-4 Raney nickel (200 mg) in methanol (50 ml) at room temperature and pressure. After 3 h, the theoretical volume of hydrogen for nitro group reduction had been absorbed; the reaction mixture was filtered through a bed of celite, and was washed through with copious amounts of methanol. The filtrate was evaporated under reduced pressure, and the residue resulting was purified by 'flash' column chromatography on silica gel (10 g) eluting with ethyl acetate-hexane (1:2) to give the anilino cyanohydrin (15) (160 mg, 95%) as a viscous oil. R_F [EtOAc-hexane (1:1)] 0.56. $C_{16}H_{26}N_2O_3Si$ requires C, 59.59; H, 8.13; N, 8.69; M 322.1712. Found: C, 59.87; H, 8.00; N, 8.96; M^+ 322.1702. δ_H 6.46 (1H, d, J = 1.7 Hz, ArH), 6.42 (1H, d, J = 1.7 Hz, ArH), 5.35 [1H, s, ArCH(OSi)CN], 3.84 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 1.8-1.4 (2H, br s, exchanges with D_2O, NH_2), 0.93 [9H, s, $(CH_3)_3CSi$], 0.21 (3H, s, CH_3Si), 0.14 (3H, s, CH_3Si); ν_{max} 3 489 (NH), 3 394 (NH), 2 954 (CH), 2 931 (CH), 2 858 (OCH_3), 1 611 (NH_2 bend), 1 600 (aromatic), 1 509 (aromatic), 1 462 cm^{-1}; λ_{max} 291 (ε = 1 200), 237.5 sh (7 800), 218 (30 400) nm; m/z 322 (33%, M^+), 265 (68, M - t-Bu), 191 (100, M - t - $BuMe_2SiO$).

5-{5-[1-(t-Butyldimethylsilyloxy)-1-cyanomethyl]-2,3-dimethoxyphenylaminomethylene}-2,2-dimethyl-1,3-dioxane-4,6-dione (16).

2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (40 mg, 0.28 mmol) and trimethyl orthoformate (10 ml) were refluxed for 2 h. Then a solution of anilino cyanohydrin (15) (80 mg, 0.25 mmol) in trimethyl orthoformate (5 ml) was added and the mixture was refluxed for a further 3 h under nitrogen. The solvent was evaporated under reduced pressure, and the residue was purified by 'flash' column chromatography on silica gel (10 g) eluting with ethyl acetate-hexane (1:2) to give the Meldrum's acid derivative (16) (110 mg, 92%) as a solid. The analytical sample was recrystallised from ethyl acetate-hexane as needles, m.p. 123-125 °C. R_F [EtOAc-hexane (1:1)] 0.57. $C_{23}H_{32}N_2O_7Si$ requires C, 57.96; H, 6.77; N, 5.88; M 476.1979. Found: C, 57.92; H, 6.92; N, 5.59; M^+ 476.1995. δ_H 11.65 (1H, br d, J = 14.6 Hz, exchanges with D_2O, NH), 8.62 (1H, d, J = 14.6 Hz, collapses to s on addition of D_2O, NH-CH=C), 7.02 (1H, d, J = 1.6 Hz, ArH), 6.91 (1H, d, J = 1.6 Hz, ArH), 5.44 [1H, s, ArCH(OSi)CN], 3.98 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 1.74 [6H, s, $(CH_3)_2C$], 0.95 [9H, s, $(CH_3)_3CSi$], 0.25 (3H, s, CH_3Si), 0.17 (3H, s, CH_3Si); δ_C 165.0, 163.2 (2 x C=O), C N), 153.5, 150.9, 139.5, 133.4, 131.9, 118.6, 107.5, 105.0 (2 x vinyl C, 6 x aromatic C), 88.2, 63.4, 61.1, 56.1 (2 x OCH_3), 27.0, 25.4, 18.1, -5.1 (CH_3Si), -5.3 (CH_3Si); ν_{max} 2 859 (OCH_3), 1 723 (lactone C=O), 1 677 (C=C), 1 614, 1 600 (aromatic), 1 507 (aromatic) cm^{-1}; λ_{max} 337 (ε = 20 000), 255 sh (6 100), 235 (12 100), 211 (19 600) nm; m/z 476 (7%, M^+), 361 (28, M - t - $BuMe_2Si$ or t - Bu - acetone), 343 (100, M - OCH_3 - CO_2 - acetone).

2-(t-Butyldimethylsilyloxy)-2-[7,8-dimethoxy-4(1H)-quinolinon-5-yl]ethanonitrile (17).

Meldrum's acid derivative (16) (1300 mg, 2.73 mmol) was refluxed in diphenyl ether (25 ml) under a stream of nitrogen on a preheated Wood's metal bath. After 5 min, the reaction mixture was cooled and was purified by 'flash' column chromatography on silica gel (150 g), applying the reaction mixture to the column with dichloromethane (5 ml), and eluting first with hexane (to remove diphenyl ether), then sequentially with ethyl acetate-hexane (1:2), (1:1), (2:1) and ethyl acetate to give the cyano quinolone (17) (902 mg, 88%). The analytical sample was recrystallised from ethyl acetate as needles, m.p. 157-159 °C. R_F (EtOAc) 0.28. $C_{19}H_{26}N_2O_4Si$ requires C, 60.94; H, 7.00; N, 7.48; M 374.1662. Found: C, 60.91; H, 7.05; N, 7.27; M^+ 374.1665. δ_H 9.35 (1H, br dd, J = 1.5 Hz, 6.0 Hz, exchanges with D_2O, NH), 7.57 (1H, dd, J = 6.0 Hz, 7.5 Hz, collapses to d, J = 7.5 Hz on addition of D_2O, 2-H), 7.55 [1H, s, ArCH(OSi)CN or 6-H], 7.11 [1H, s, 6-H or ArCH(OSi)CN], 6.15 (1H, dd, J = 1.5 Hz, 7.5 Hz, collapses to d, J = 7.5 Hz on D_2O shake, 3-H), 3.99 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 0.97 [9H, s, $(CH_3)_3CSi$], 0.28 (3H, s, CH_3Si), 0.15 (3H, s, CH_3Si); δ_C 179.8 (C=O), 152.2 (CN), 138.3, 136.2, 135.8, 133.3, 119.8, 116.9, 110.0, 107.7 (8 x aromatic C), 61.3 [ArCH(OSi)CN], 60.7 (OCH_3), 55.8 (OCH_3), 25.3 [$(CH_3)_3C$], 17.9 [$(CH_3)_3CSi$], -5.5 (CH_3Si), -5.6 (CH_3Si); ν_{max} 3 419 (NH), 2 992, 2 955 (CH), 2 887, 2 859 (OCH_3), 1 629 (quinolone), 1 616 (quinolone), 1 591 (aromatic), 1 532, 1 506 (aromatic), 1 457, 1 388 (t - Bu), 1 366 (t - Bu) cm^{-1}; λ_{max} 332 (ε = 9 500), 322 (10 200), 263 (19 900), 255 (18 000), 227 (31 600) nm; m/z 374 (25%, M^+), 359 (13, M - CH_3), 317 (100, M - t - Bu); FAB 375 (MH^+).

5-[2-Amino-1-(t-butyldimethylsilyloxy)ethyl]-7,8-dimethoxy-4(1H)-quinolinone (18).

Cyanoquinolone (17) (1.40 g, 3.74 mmol) was hydrogenated in methanol (150 ml) at room temperature and pressure, with freshly prepared W-4 Raney nickel as catalyst. After 12 h the reaction mixture was filtered through celite, washed through with copious amounts of methanol, and the filtrate was evaporated under reduced pressure. The residue resulting was recrystallised from methanol to give the aminoethyl quinolone (18) (1.29 g, 91%) as rods, m.p. 192-194 °C. R_F [EtOAc-MeOH (9:1) + drops NH_3 conc.] 0.10. δ_H 9.30 (1H, v br, NH), 7.50 (1H, d, J = 7.4 Hz, 2-H), 7.37 (1H, s, 6-H), 6.38 [1H, dd, J = 3.0 Hz, 5.8 Hz, ArCH(OSi)CH_2], 6.11 (1H, d, J = 7.4 Hz, 3-H), 3.95 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.00 [1H, br dd, J = 3.0 Hz, 13.3 Hz, ArCH(OSi)$CH_AH_BNH_2$], 2.61 [1H, br dd, J = 5.8 Hz, 13.3 Hz, ArCH(OSi)$CH_AH_BNH_2$], 1.31 (2H, br, NH_2), 0.93 [9H, s, $(CH_3)_3CSi$], 0.09 (3H, s, CH_3Si), -0.09 (3H, s, CH_3Si). On D_2O shake, signals at 9.30 and 1.31 disappear and the br dd's at 3.00 and 2.61 sharpen to dd's; ν_{max} 3 416 (NH), 3 250 (NH), 2 938, 2 928 (CH), 2 852 (OCH_3), 1 627 (quinolone), 1 611 (quinolone), 1 584 (aromatic), 1 530, 1 515, 1 508 (aromatic), 1 457, 1 388 (t-Bu), 1 360 (t-Bu), 1 280, 1 159, 1 110, 1 093 cm^{-1}; λ_{max} (MeOH) 334 (ε = 10 400), 322 (11 800), 263 (24 500), 255 (21 400), 226 (35 600) nm; m/z $C_{19}H_{30}N_2O_4Si$ requires (M^+-CH_3) 363.1740, found 363.1730; $C_{19}H_{30}N_2O_4Si$ requires (M^+-H_2O) 360.1869, found 360.1862. 363 (0.2%, M^+-CH_3), 360 (3.1, M - H_2O), 349 (18, M - CHO), 75 (100).

4H-6-(t-Butyldimethylsilyloxy)-5,6-dihydro-8,9-dimethoxybenzo[de][1,6]naphthyridine (19).

Aminoethylquinolone (18) (200 mg, 0.53 mmol) and p-toluenesulphonic acid monohydrate (10 mg, 0.05 mmol) were added to 1,1,1,3,3,3-hexamethyldisilazane (5

ml), and solvation was aided by sonication for 15 min, then the reaction mixture was refluxed under nitrogen for 8 h. The solvent was evaporated under reduced pressure; methanol (50 ml) was added and the solution was stirred for 30 min to deprotect any N-silylated material. The solvent was evaporated under reduced pressure, and the residue was purified by 'flash' column chromatography on silica gel (15 g) eluting with ethyl acetate-methanol (9:1) containing 1% conc. ammonia solution to give the tricyclic silyloxy compound (**19**) (101 mg, 53%) as a clear gum which rapidly turned pink on exposure to air. R_F [EtOAc-MeOH (9:1) + drops NH_3 conc.] 0.37. δ_H (d_6-DMSO) 8.25 (1H, d, J = 5.4 Hz, 2-H), 7.69 (1H, br s, NH), 7.18 (1H, s, 7-H), 6.42 (1H, d, J = 5.4 Hz, 3-H), 5.05 [1H, dd, J = 5.0 Hz, 8.0 Hz, ArCH(OSi)CH_2], 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.54 [1H, dd, J = 5.0 Hz, 12.1 Hz, ArCH(OSi)CH_AH_B], 3.20 [1H, dd, J = 8.0 Hz, 12.1 Hz, ArCH(OSi)CH_AH_B], 0.92 [9H, s, $(CH_3)_3C$], 0.18 (3H, s, CH_3Si), 0.15 (3H, s, CH_3Si); ν_{max} 3 414 (NH), 2 953, 2 933 (CH), 2 857 (OCH_3), 1 626 (aminoquinoline), 1 582 (aromatic), 1 547, 1 530, 1 519, 1 460, 1 426, 1 418, 1 381 (t-Bu), 1 328, 1 309 cm^{-1}; m/z $C_{19}H_{28}N_2O_3Si$ requires M^+ 360.1869, found 360.1874; requires (M^+-H) 359.1791, found 359.1806. 360 (1.2%, M^+), 359 (15, M-H), 345 (5, M - CH_3), 303 (1, M - t-Bu), 84 (100, d_6-DMSO), 57 (75, t-Bu^+); FAB 361 (MH^+).

Hydrochloride of Aaptamine (1).

Method 1. Aminoethylquinolone (**18**) (500 mg, 1.32 mmol) and p-toluenesulphonic acid (25 mg, 0.13 mmol) were added to 1,1,1,3,3,3-hexamethyldisilazane (15 ml). The mixture was sonicated for 15 min, and then refluxed under nitrogen. After 12 h, the solvent was evaporated under reduced pressure, then methanol (100 ml) and concentrated hydrochloric acid (5 ml) were added to deprotect any N-silylated material. After 2 h, the solvent was evaporated under reduced pressure and methanol (50 ml) was added. A stream of hydrogen chloride gas was bubbled through the resulting solution for 30 min, and the flask stoppered. After 12 h, the solution had turned bright yellow; the solvent was evaporated under reduced pressure, and the residue was purified by 'flash' column chromatography on silica gel (50 g) eluting with chloroform-methanol (8:2) under an atmosphere of nitrogen. The crude product was recrystallised from methanol-acetone to give aaptamine hydrochloride (**1**) (180 mg, 51%) as small yellow needles, m.p. 105-107 °C (lit.,[1] m.p. 110-113 °C; synthetic[2,3,4] m.p. 107 °C, 114-121 °C, 105-107 °C). R_F [$CHCl_3$-MeOH (4:1)] 0.33. δ_H (d_6-DMSO) 13.18 (1H, br d, $J_{4,5}$ = 5.2 Hz, H-4), 12.32 (1H, br d, $J_{1,2}$ = 6.2 Hz, H-1), 7.85 (1H, dd, $J_{1,2}$ = 6.2 Hz and $J_{2,3}$ = 6.6 Hz, H-2), 7.39 (1H, dd, $J_{4,5}$ = 5.2 Hz and $J_{5,6}$ = 7.1 Hz, H-5), 7.12 (1H, s, H-7), 6.88 (1H, d, $J_{5,6}$ = 7.1 Hz, H-6), 6.50 (1H, d, $J_{2,3}$ = 6.6 Hz, H-3), 4.03 (3H, s, CH_3O-8), 3.86 (3H, s, CH_3O-9); δ_C (D_2O) 157.1 (s, C-8), 149.4 (s, C-3a), 141.4 (d, C-2), 133.2 (s, C-9a), 132.7 (s, C-6a), 131.2 (s, C-9), 129.2 (d, C-5), 115.9 (s, C-9b), 113.5 (d, C-7), 101.4 (d, C-6), 98.4 (d, C-3), 61.1 (q, CH_3O-9), 57.0 (q, CH_3O-8); ν_{max} (KBr disc) 3 427 br (NH), 3 145, 3 079, 3 017, 2 924 (CH), 2 855 (OCH_3), 1 655, 1 623, 1 610, 1 551, 1 466, 1 429, 1 385, 1 350, 1 325, 1 246, 1 198, 1 113, 1 097, 1 026, 966, 783 cm^{-1}; λ_{max} (H_2O) 393 sh (ϵ = 5 900), 383 (6 200), 352 sh (4 600), 310 (4 700), 256 (22 500), 236 (19 700), 215 (18 800) nm; m/z $C_{13}H_{12}N_2O_2$ requires M^+ 228.0886, found 228.0892; 228 (51.71%, M^+), 213 (M-CH_3, 92), 142 (100); FAB 229 (MH^+).

Method 2. The tricyclic silyloxy compound (**19**) (85 mg, 0.24 mmol) was desilylated by treatment with concentrated hydrochloric acid (0.25 ml) in ethanol

(25 ml) at room temperature for 2 h. After evaporation under reduced pressure the residue was dissolved in water (50 ml) and extracted with dichloromethane (2 x 50 ml). The aqueous solution was evaporated and the residue dissolved in methanol (10 ml); hydrogen chloride was bubbled through for 30 min and the stoppered flask allowed to stand for 12 h. The resulting yellow solution was evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel (10 g) eluting with chloroform-methanol (4:1) to give aaptamine hydrochloride (34 mg).

ACKNOWLEDGEMENTS

We are indebted to SERC, Imperial Chemical Industries, Trinity College and Roche Products Limited for support. We warmly thank Professor M.P. Cava and Dr M.V. Lakshmikantham for sample provision.

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